(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 October 2003 (16.10.2003)

PCT

(10) International Publication Number
WO 03/084611 A1

(51) International Patent Classification[7]: A61P 35/00, A61K 38/15

(21) International Application Number: PCT/JP03/03823

(22) International Filing Date: 27 March 2003 (27.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/369,868 5 April 2002 (05.04.2002) US

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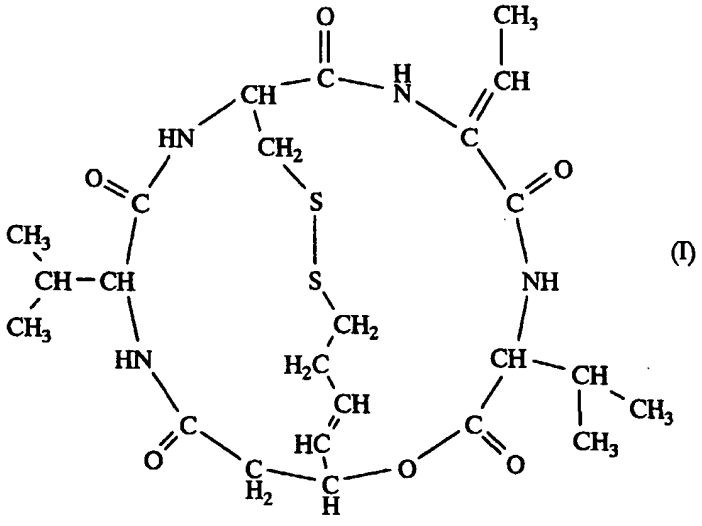
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DEPSIPEPTIDE FOR THERAPY OF KIDNEY CANCER



(I)

(57) Abstract: The present invention provides a therapeutic agent of kidney cancer, which comprises FK228 of the formula (I) or a salt thereof. FK228 or a salt thereof, which is an active ingredient in the present invention, shows a superior antitumor activity in vivo against kidney cancer.

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DESCRIPTION

DEPSIPEPTIDE FOR THERAPY OF KIDNEY CANCER

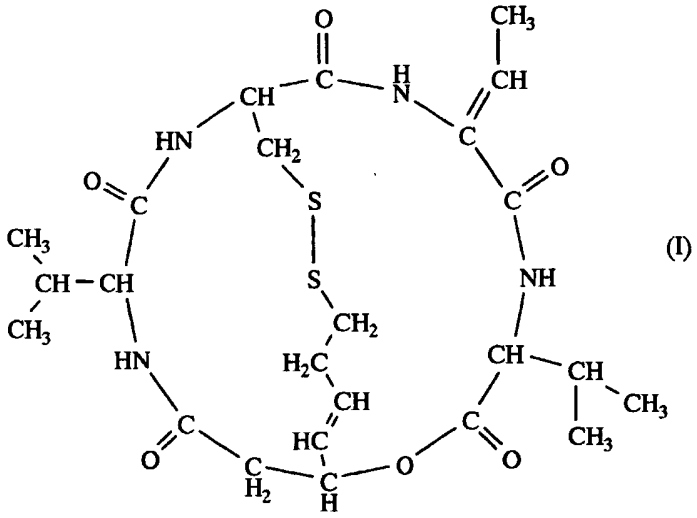
Technical field

The present invention relates to a method of treating kidney cancer and a therapeutic agent of Kidney cancer.

Background Art

It has been pointed out that substances and compounds reported to have an antitumor activity based only on *in vitro* data alone generally do not allow anticipation of their effects in the *in vivo* results. In other words, a substance showing an antitumor activity *in vitro* does not necessarily show an antitumor activity also *in vivo*, and therefore, the application of a substance showing an antitumor activity *in vitro* directly as an anti-cancer agent is problematic.

For example, it has been reported that a compound (Sequence Listing SEQ ID NO. 1) of the formula (I)



(I)

induces a strong antitumor activity by selectively inhibiting histone deacetylase. It has been also reported that this substance causes high acetylation of histone in the cells treated with this substance, and as a result, induces a transcription controlling activity of various genes, a cell cycle inhibitory activity and an apoptosis inhibitory activity

(JP-B-7-64872, H. Nakajima *et al.*, Exp. Cell Res. 241, 126-133 (1998)). As the situation stands, however, there are many problems yet to be solved, such as effectiveness of *in vitro* results in *in vivo* application, *in vivo* effectiveness against any tumor and the like. The antitumor activity *in vitro* against kidney cancer has been reported, but an antitumor activity *in vivo* against kidney cancer has not been reported.

Histone deacetylase is a metallo deacetylase having Zn coordinated at the active center (M.S. Finnin *et al.*, Nature, 401, 188-193 (1999)). This enzyme is considered to change affinity of various acetylated histones for DNA. The direct biological phenomenon provided thereby is a change in the chromatin structure. The minimum unit of the chromatin structure is a nucleosome wherein a 146 bp DNA winds around a histone octamer (H2A, H2B, H3 and H4, 2 molecules each, core histone) 1.8 times counterclockwise. The core histone stabilizes the nucleosome structure as the positive charge of the N-terminal of each histone protein interacts with DNA. The acetylation of histone is controlled by the equilibrium relationship between acetylation reaction, in which histone acetyltransferase is involved, and the deacetylation reaction, in which histone deacetylase is involved. The acetylation of histone occurs in an evolutionarily well-conserved lysin residue in the N-terminal of a histone protein, whereby, it is considered, the core histone protein loses the charge of the N-terminal, the interaction with DNA decreases, and the structure of nucleosome is instabilized. Conversely, therefore, deacetylation of histone is considered to stabilize the nucleosome structure. However, the degree of changes in the chromatin structure caused by the acetylation is unclear nor is it clear how it is related to the secondarily induced control of transcription.

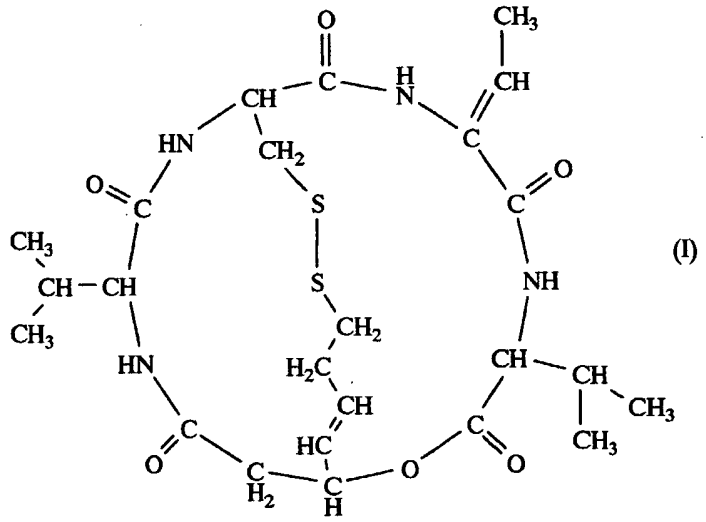
Disclosure of The Invention

The present inventors have conducted intensive studies

in an attempt to solve the above-mentioned problems, and found a therapeutic agent for kidney cancer, which is capable of confirming its antitumor effect *in vivo*, particularly in human patients with kidney cancer, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

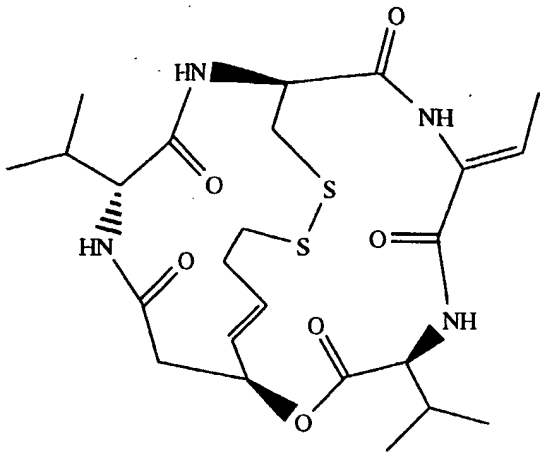
(1) A method of treating kidney cancer in mammals, which comprises administering an effective amount of a compound of the formula (I)



(I)

or a salt thereof to a mammal.

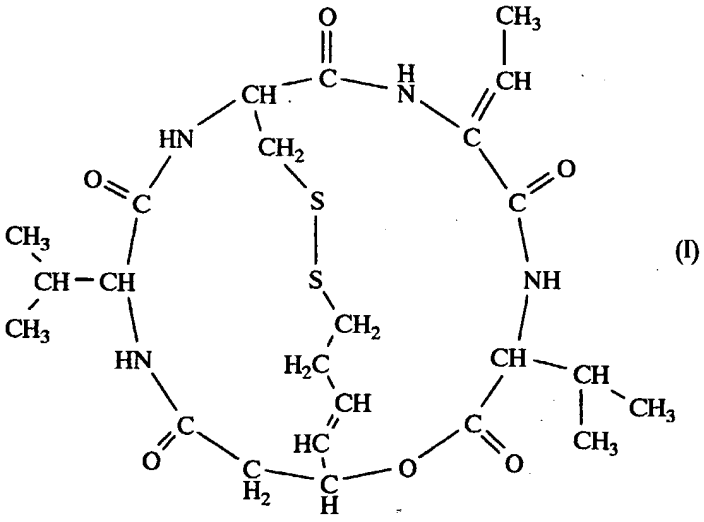
(2) The treatment method of kidney cancer according to the above-mentioned (1), wherein the compound of the formula (I) is a compound of the formula (II)



(II)

(3) The treatment method of kidney cancer according to the above-mentioned (1), wherein the mammal is a human.

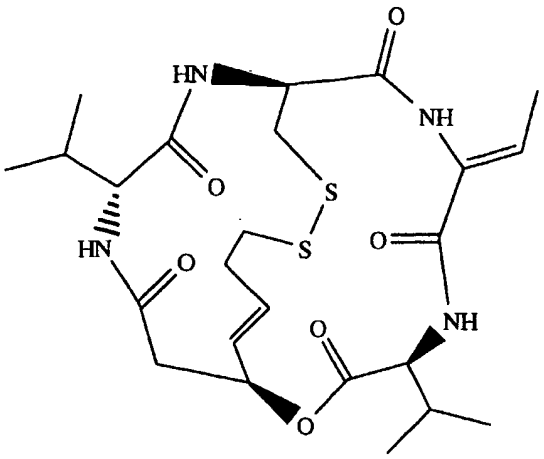
(4) A method of suppressing growth of a cancerous tumor of the kidney in mammals, which comprises administering an effective amount of a compound of the formula (I)



(I)

or a salt thereof to a mammal.

(5) The method of suppressing growth of the cancerous tumor of the kidney according to the above-mentioned (4), wherein the compound of the formula (I) is a compound of the formula (II)

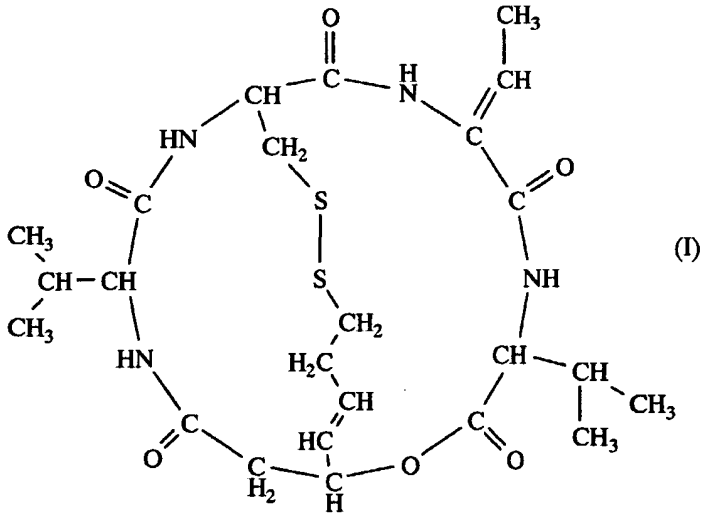


(II)

(6) The method of the above-mentioned (4) for suppressing the growth of the cancerous tumor of the kidney *in vivo*.

(7) The method of the above-mentioned (6), wherein the *in vivo* means in a body of a human.

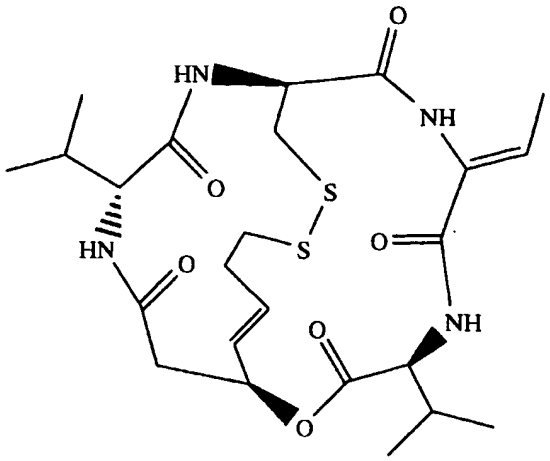
(8) A therapeutic agent of kidney cancer, which comprises, as an active ingredient, a compound of the formula (I)



(I)

or a salt thereof.

(9) The therapeutic agent according to the above-mentioned (8), wherein the compound of the formula (I) is a compound of the formula (II)

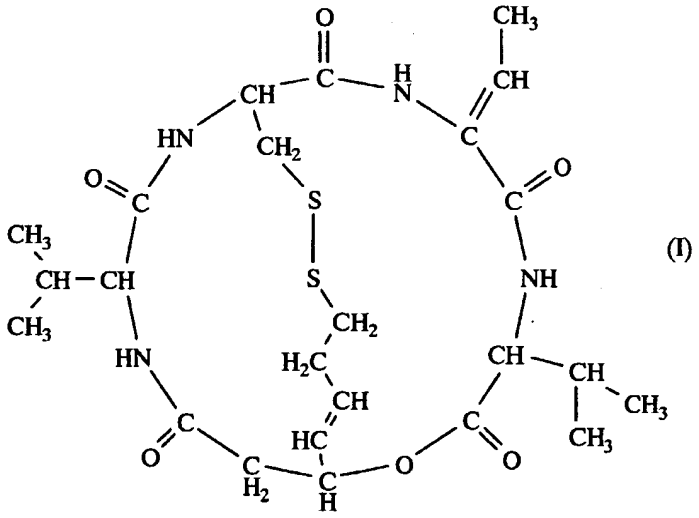


(II)

(10) The therapeutic agent according to the above-mentioned (8), which has an antitumor activity *in vivo*.

(11) The therapeutic agent according to the above-mentioned (8), which is used for a human.

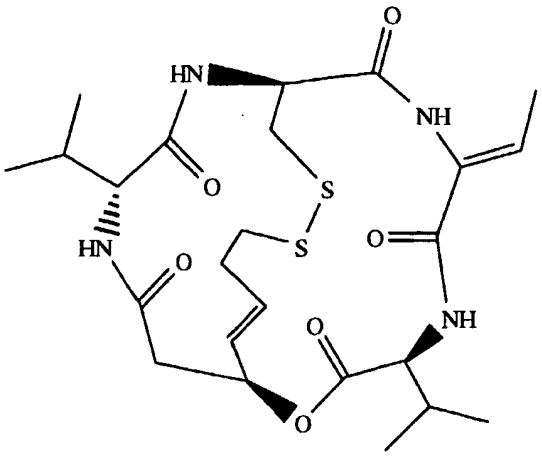
(12) Use of a compound of the formula (I)



(I)

or a salt thereof, for the production of a therapeutic agent of kidney cancer.

(13) The use according to the above-mentioned (12), wherein the compound of the formula (I) is a compound of the formula (II)

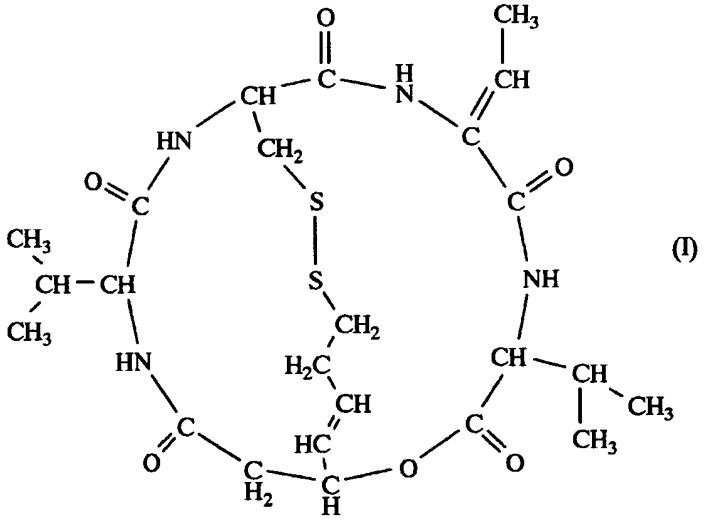


(II)

(14) The use according to the above-mentioned (12), wherein the above-mentioned therapeutic agent of kidney cancer has an antitumor activity *in vivo*.

(15) The use according to the above-mentioned (12), wherein the above-mentioned therapeutic agent of kidney cancer is used for a human.

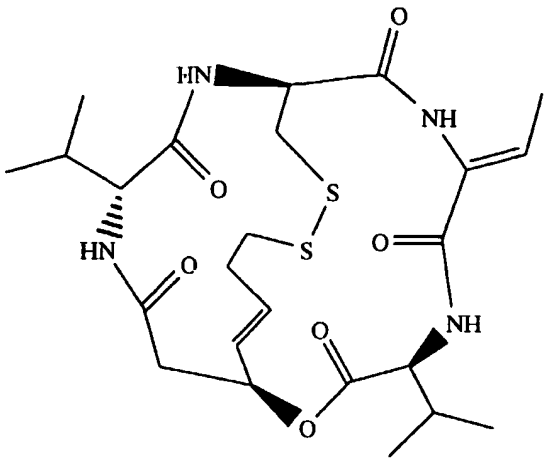
(16) A pharmaceutical composition for treating kidney cancer, which comprises a compound of the formula (I)



(I)

or a salt thereof, and a pharmaceutically acceptable carrier.

(17) The pharmaceutical composition of the above-mentioned (16), wherein the compound of the formula (I) is a compound of the formula (II)



(II)

(18) The pharmaceutical composition of the above-mentioned (16), which has an antitumor activity *in vivo*.

(19) The pharmaceutical composition of the above-mentioned (16), which is used for a human.

(20) A commercial package comprising a pharmaceutical composition of any of the above-mentioned (16) to (19) and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for treating kidney cancer.

Brief Description Of The Drawing

Fig. 1 is a graph showing the antitumor activity of FR901228 against human kidney tumor (RXF-631L) transplanted in mouse.

Detailed Description Of The Invention

The therapeutic agent of kidney cancer of the present invention contains, as an active ingredient, a compound of the formula (I) (hereinafter to be also referred to as FK228) or a salt thereof. The treatment method of kidney cancer of the present invention includes administering an effective amount of FK228 to mammals inclusive of human. Of the compounds of the formula (I), preferred is a compound of the formula (II), which is a stereoisomer (hereinafter to be also referred to as FR901228). These compounds have a potent histone deacetylase inhibitory activity (Nakajima, H. *et al.*; *ibid* (1998)), and

particularly FR901228 has an even more potent histone deacetylase inhibitory activity. Therefore, it is suitably included in the therapeutic agent of kidney cancer of the present invention, and can be suitably used for the treatment method of kidney cancer of the present invention.

Unless otherwise specified, a simple reference to FK228 in the present specification means a group of compounds, irrespective of the stereoisomerism, including a compound of the formula (II).

FK228 and a salt thereof are known substances and are obtainable. For example, FR901228, which is one of the stereoisomers of FK228, can be obtained by culturing, under aerobic conditions, a bacterial strain belonging to the genus *Cromobacterium*, which is capable of producing FR901228, and recovering the substance from the culture broth. The bacterial strain belonging to the genus *Cromobacterium*, which is capable of producing FR901228, is exemplified by *Cromobacterium violaceum* WB968 (FERM BP-1968). An FR901228 substance can be obtained from this production cell according to the disclosure of JP-B-7-64872. It is preferable to obtain FR901228 from a bacterial strain belonging to the genus *Cromobacterium*, which is capable of producing FR901228, because FR901228 can be obtained more easily. However, synthetic or semi-synthetic FR901228 is also advantageous because an additional purification step is not necessary or can be made simple. Similarly, FK228 other than FR901228 can be synthesized or semi-synthesized by a method conventionally known. To be specific, it can be produced according to the method reported by Khan W. Li, *et al.* (J. Am. Chem. Soc., vol. 118, 7237-7238 (1996)).

The salt of FK228 is a biologically acceptable salt, which is generally non-toxic, and is exemplified by salts with base or acid addition salts, inclusive of salts with inorganic base such as alkali metal salt (e.g., sodium salt, potassium

salt etc.), alkaline earth metal salt (e.g., calcium salt, magnesium salt etc.), ammonium salt, salts with organic base such as organic amine salt (e.g., triethylamine salt, diisopropylethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt etc.), inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate etc.), organic carboxylic • sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate etc.), salt with basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid etc.), and the like.

FK228 has stereoisomers based on asymmetric carbon atom and double bond, such as optical isomer, geometric isomer and the like, all of which and mixtures thereof are also encompassed in the present invention.

Further, solvate compounds (e.g., inclusion compound such as hydrate etc.) of FK228, FR901228 and salts thereof are also encompassed in the present invention.

In the present invention, *in vivo* and *in vitro* means as these terms are used in this field. That is, "*in vivo*" means that the target biological functions and responses are expressed in the body, such as in the body of various mammals to be mentioned below, preferably in the body of a human. The term "*in vitro*" means that such functions and responses are expressed in test tubes including tissue culture system, cell culture system, cell free system and the like.

FK228, which is a histone deacetylase inhibitor, exerts an antitumor activity against various tumors. Among others, it shows a noticeable effect *in vivo* and in human against kidney cancer.

The therapeutic agent of kidney cancer of the present invention can be used for mammals such as human, dog, bovine,

horse, rat, guinea pig and the like.

The therapeutic agent of kidney cancer of the present invention can be used in the form of a solid, semi-solid or liquid pharmaceutical preparation containing FK228 or a salt thereof as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for oral or parenteral application. The active ingredient can be admixed with a typical, non-toxic pharmaceutically acceptable carrier suitable for the dosage form, such as powder, tablet, pellet, capsule, suppository, liquid, emulsion, suspension, aerosol, spray and other form for use. Where necessary, auxiliary agent, stabilizer, tackifier and the like may be used. These carriers and excipients may be sterilized where necessary, or a sterilization treatment may be applied after formulation into a preparation. FK228 and a salt thereof are contained in the therapeutic agent of kidney cancer in an amount sufficient to produce a therapeutic effect on kidney cancer, such as suppression of infiltration into surrounding tissues, metastasis to a distal part, and growth of cancer.

The method of administering the therapeutic agent of kidney cancer of the present invention is free of any particular limitation as long as it can provide a therapeutic effect on kidney cancer described above. Particularly when the therapeutic agent of kidney cancer of the present invention is used, parenteral administration is preferable, namely, intravenous administration, intramuscular administration, direct administration into the tissue, administration into nostril cavity, intradermal administration, administration into cerebrospinal fluid, administration into biliary tract, intravaginal administration and the like. In addition, a liposome method and the like can be preferably used. When this therapeutic agent is applied to a human, intravenous administration, intramuscular administration or oral administration is preferably employed for the application. A

therapeutically effective amount of the active ingredient, FK228 or a salt thereof, varies depending on the age and condition of individual patients to be treated, and the type of cancer. In the case of intravenous administration, the daily dose of FK228 is generally 0.1-100 mg, preferably 1-50 mg, more preferably 5-30 mg, per m^2 of the body surface area of human, which is continuously administered by infusion to treat the tumor. The time of continuous administration by infusion varies depending on the dose. It is preferably 3-6 h, more preferably 3.5-4.5 h, most preferably 4 h. The administration frequency is based on a cycle containing 1 to 4 times of administration(s) at 18-30 day intervals, and 2 to 7 such cycles are preferably applied. Additionally, the combination treatment with FK228 and retinoic acid (preferably all-trans-retinoic acid: ATRA) is also preferable.

The present invention is described in more detail in the following by way of Examples. The present invention is not limited in any way by these Examples.

Example 1: antitumor effect of FK228 on human renal tumor xenograft

(1) Preparation of drug

A recommended amount of FR901228 was weighed, a solvent (10% HCO-60 (Nihon Surfactant Kogyo K.K./saline) was added and the mixture was ultrasonicated for dissolution. The positive control substance, Taxol, was dissolved in Cremophor EL (SIGMA/ethanol (1:1)) to a concentration of 24 mg/mL before test and preserved in refrigerator. When in use, a 9-fold amount of physiological saline was added to dilute the substance to 2.4 mg/mL (solvent component: 5% Cremophor EL-5% ethanol-90% saline).

(2) Animals

For the antitumor activity test of the drug, BALB/cANnNCrj-nu/nu mice (female, 6-week-old) were purchased from Charles River Japan (Yokohama, Japan), and after

acclimation for more than 1 week, subjected to the test. The mice were reared in an SPF environment, where free access to water and feed was allowed.

(3) Tumor

2-3×10^7 Human renal tumor (RXF-631L: Cancer Chemotherapy Center, Japan Foundation for Cancer Research, Tokyo, Japan) was maintained subcutaneously by serial passage in BALB/cANnNCrj-nu/nu mice.

(4) Experimental implantation and grouping

Fragments (3×3×3 mm) of RXF-631L tumor were subcutaneously implanted into the right flank of BALB/cANnNCrj-nu/nu mice. When the tumor volume reached 100-300 mm^3 after the tumor implantation, the mice were grouped (6 per group) avoiding dispersion in the tumor volume. The tumor volume was calculated from the formula: tumor volume (mm^3)= 1/2×L×W^2 where L and W represent the length and width of the tumor mass, respectively.

(5) Administration

The administration was started on the day the mice were grouped (Day 0). FR901228 (3.2 and 1.8 mg/kg) was intravenously administered to the FR901228 administration group 3 times every 4 days (q4d×3). The positive control substance, Taxol, was intravenously administered (24 mg/kg) to the Taxol administration group for 5 consecutive days (qd×5). The solvent alone (10% HCO-60/saline) was administered to the control group (q4d×3). The liquid amount of administration was calculated based on the body weight measured on the day of administration (0.1 mL/10 g body weight). The MTD (maximum tolerance dose) of FR901228 and Taxol was 3.2 mg/kg/day (q4d×3) and 24 mg/kg/day (qd×5), respectively.

(6) Measurement of tumor size and body weight

The tumor size (length, width) and body weight were measured twice a week from Day 0.

The results are shown in Fig. 1, wherein -●- shows a

shift in the size of tumor in the control group, -■- shows that by the administration of 1.8 mg/kg of FR901228, -▲- shows that by the administration of 3.2 mg/kg of FR901228 and -◆- shows that by the administration of 24 mg/kg of Taxol.

FR901228 suppressed the growth of human kidney cancer *in vivo*.

Example 2: Antineoplastic response

One patient (Patient Number 31-00-83-2) demonstrated a partial response. This patient was a 38-years-old female with a history of clear cell renal carcinoma that was diagnosed in 1996. The patient received a total of 10 doses of FR901228: FR901228 was administered at 9.10 mg/m^2 on day 1 and day 5 of the first cycle (21 days), 9.10 mg/m^2 on day 1 of the second cycle (21 days), 9.10 mg/m^2 on day 1 and day 5 of the third cycle (28 days), 9.10 mg/m^2 on day 1 of the fourth cycle (22 days), 12.70 mg/m^2 on day 1 of the fifth cycle (20 days), 17.8 mg/m^2 on day 1 of the sixth cycle (23 days), 17.8 mg/m^2 on day 1 of the seventh cycle (23 days) and 17.8 mg/m^2 on day 1 of the eighth cycle (21 days) by continuous infusion for 4 hours. The treatment effect was evaluated based on the RECIST criteria. This patient experienced a partial response after the first two cycles and disease progression was noted after cycle 8.

Industrial Applicability

The therapeutic agent of kidney cancer of the present invention comprising FK228 (particularly FR901228) or a salt thereof, having a histone deacetylase inhibitory activity, as an active ingredient shows a superior antitumor activity not only *in vitro* but also *in vivo*. The therapeutic agent of kidney cancer of the present invention shows a superior antitumor activity in human patients with kidney cancer. Therefore, the present invention can be suitably applied for the treatment of kidney cancer.

Free-text of Sequence Listing

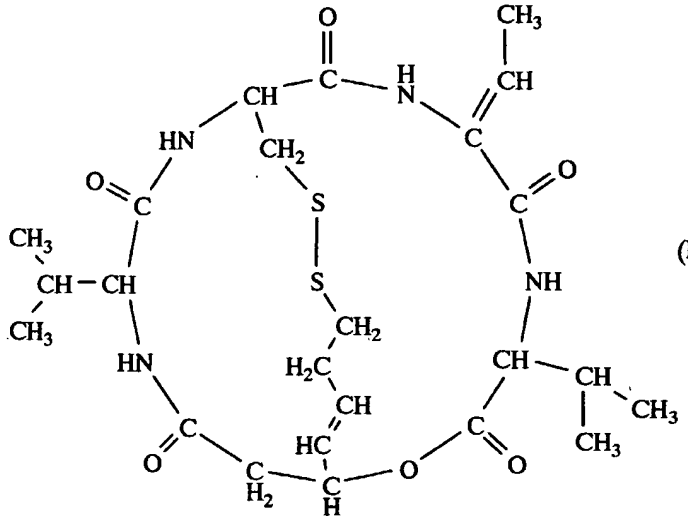
SEQ ID NO: 1: Xaa is an amino acid represented by the formula $NH_2C(CHCH_3)COOH$. In the formula $COOHCH_2CH(CHCHC_2H_4SH)OH$, the

carboxylic group is bonded with the amino group of the first amino acid Val, the hydroxyl group is bonded with the carboxylic group of the fourth amino acid Val, and the SH group is bonded with the SH group of the second amino acid Cys via a disulfide bond.

This application is based on a patent application No. 60/369,868 filed in U.S., the contents of which are hereby incorporated by reference.

CLAIMS

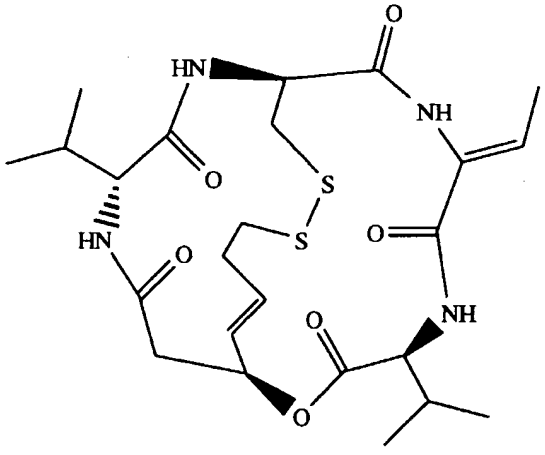
1. A method of treating kidney cancer in mammals, which comprises administering an effective amount of a compound of the formula (I)



(I)

or a salt thereof to a mammal.

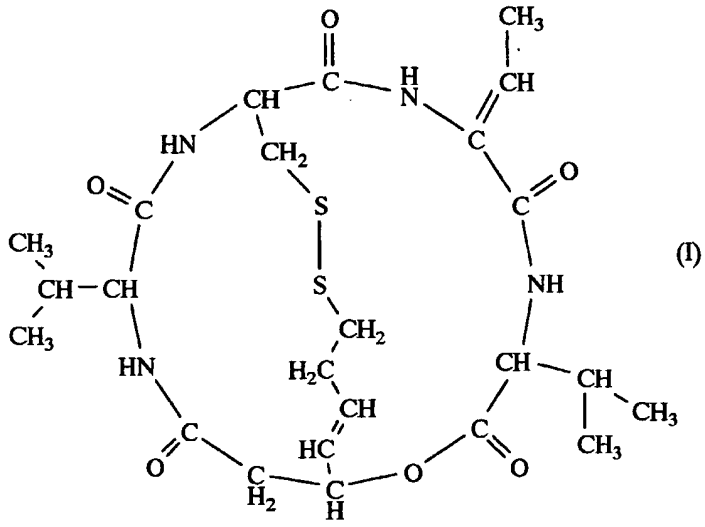
2. The treatment method of kidney cancer according to claim 1, wherein the compound of the formula (I) is a compound of the formula (II)



(II)

3. The treatment method of kidney cancer according to claim 1, wherein the mammal is a human.

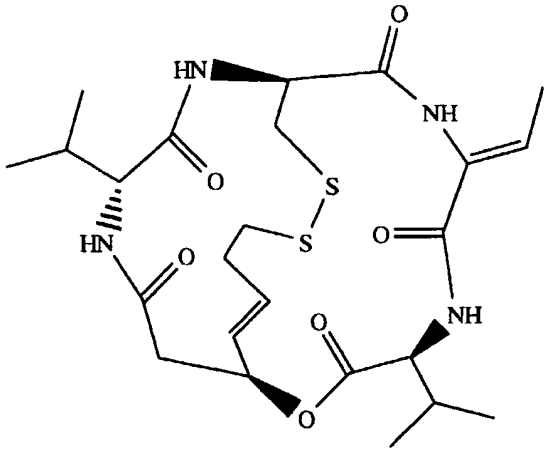
4. A method of suppressing growth of a cancerous tumor of the kidney in mammals, which comprises administering an effective amount of a compound of the formula (I)



(I)

or a salt thereof to a mammal.

5. The method of suppressing growth of the cancerous tumor of the kidney according to claim 4, wherein the compound of the formula (I) is a compound of the formula (II)



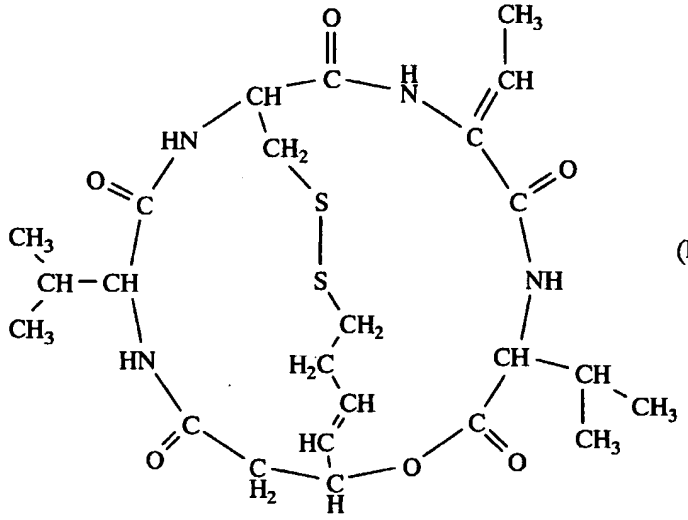
(II)

6. The method of claim 4 for suppressing the growth of the cancerous tumor of the kidney *in vivo*.

7. The method of claim 6, wherein the *in vivo* means in a body

of a human.

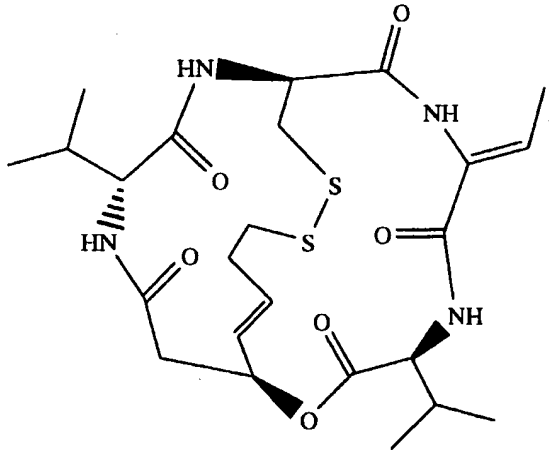
8. A therapeutic agent of kidney cancer, which comprises, as an active ingredient, a compound of the formula (I)



(I)

or a salt thereof.

9. The therapeutic agent according to claim 8, wherein the compound of the formula (I) is a compound of the formula (II)



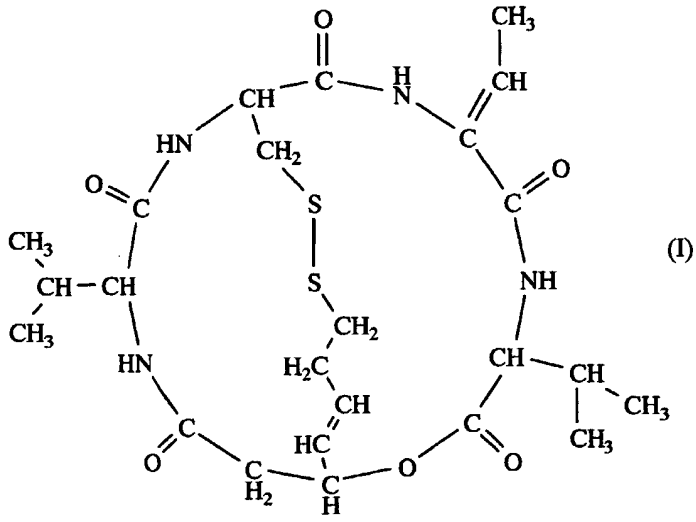
(II)

10. The therapeutic agent according to claim 8, which has an antitumor activity *in vivo*.

11. The therapeutic agent according to claim 8, which is used

for a human.

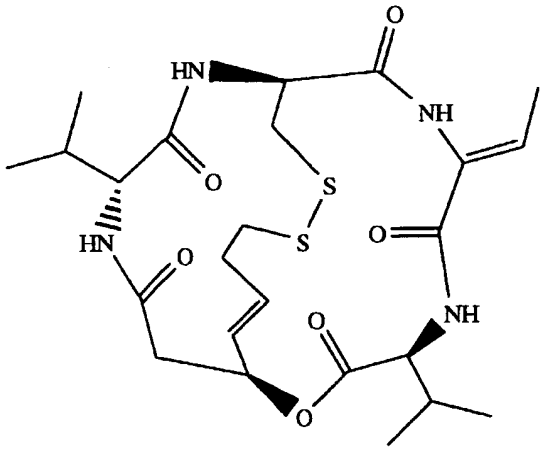
12. Use of a compound of the formula (I)



(I)

or a salt thereof, for the production of a therapeutic agent of kidney cancer.

13. The use according to claim 12, wherein the compound of the formula (I) is a compound of the formula (II)

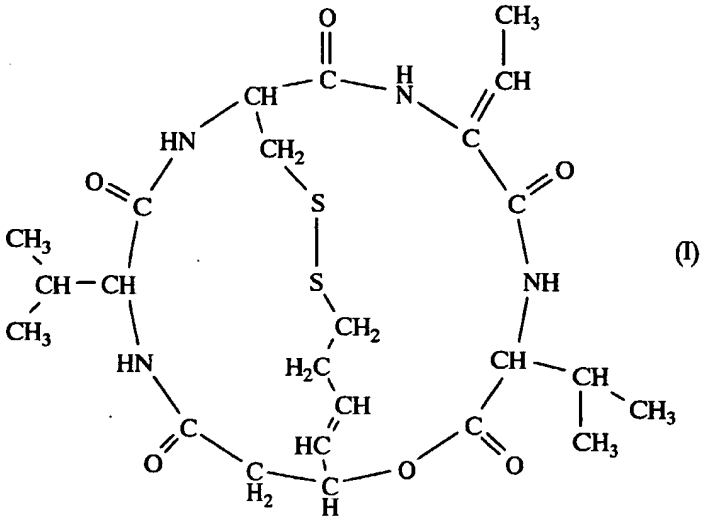


(II)

14. The use according to claim 12, wherein the above-mentioned therapeutic agent of kidney cancer has an antitumor activity *in vivo*.

15. The use according to claim 12, wherein the above-mentioned therapeutic agent of kidney cancer is used for a human.

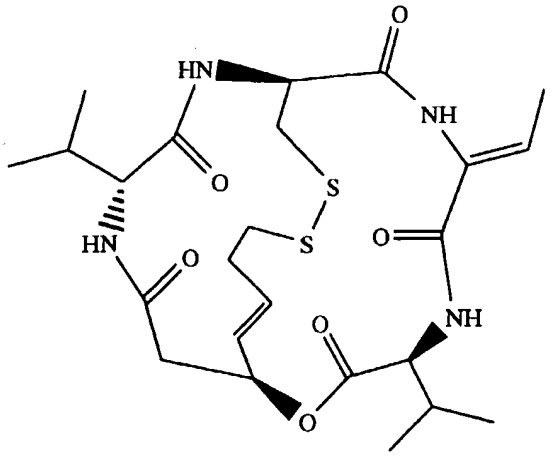
16. A pharmaceutical composition for treating kidney cancer, which comprises a compound of the formula (I)



(I)

or a salt thereof, and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, wherein the compound of the formula (I) is a compound of the formula (II)



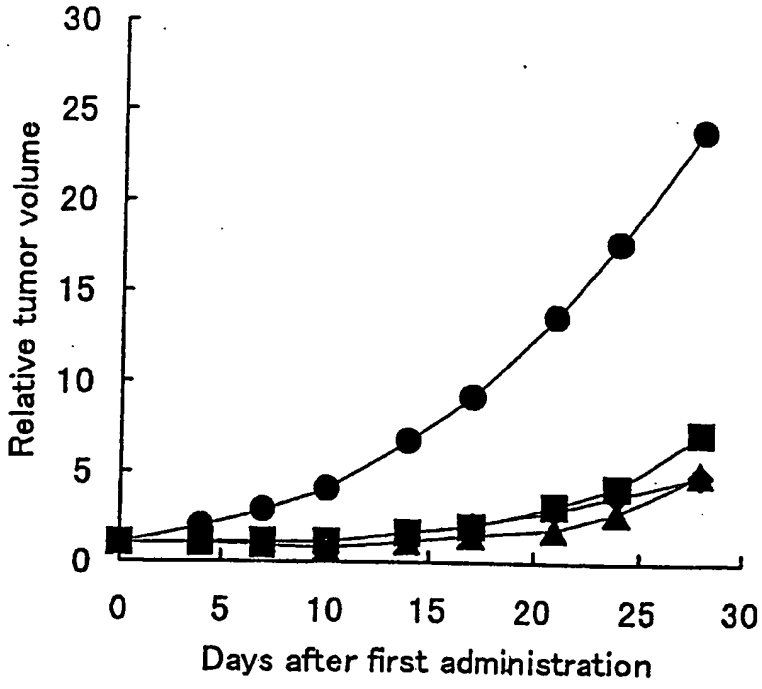
(II)

18. The pharmaceutical composition of claim 16, which has an antitumor activity *in vivo*.

19. The pharmaceutical composition of claim 16, which is used for a human.

20. A commercial package comprising a pharmaceutical composition of any of claims 16 to 19 and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for treating kidney cancer.

FIG. 1


Relative tumor volume
30
25
20
15
10
5
0
0
5
10
15
20
25
30
Days after first administration

SEQUENCE LISTING

<110> FUJISAWA PHARMACEUTICAL CO., LTD.

<110> THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by the Secretary, Department of Health and Human Services

<120> TREATMENT METHOD AND THERAPEUTIC AGENT OF KIDNEY CANCER

<130> 09537

<150> US60/369,868

<151> 2002-04-05

<160> 1

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<211> 4

<212> PRT

<213> Chromobacterium sp.

<220>

<223> Inventor: Yoshinori Naoe

<223> Inventor: Susan E. Bates

<220>

<221> SITE

<222> (3)

<223> Xaa is an amino acid represented by the formula $NH_2C(CHCH_3)COOH$.

<220>

<221> SITE

<222> (1), (2), (4)

<223> In the formula $COOHCH_2CH(CHCHC_2H_4SH)OH$, the

carboxylic group is bonded with the amino group of the first amino acid Val, the hydroxyl group is bonded with the carboxylic group of the fourth amino acid Val, and the SH group is bonded with the SH group of the second amino acid Cys via a disulfide bond.

<400> 1

Val Cys Xaa Val 4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 03/03823

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P35/00 A61K38/15

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, FSTA, BIOSIS, CHEM ABS Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 085400 A (DIMARTINO JORGE ;SUPERGEN INC (US)) 31 October 2002 (2002-10-31) claims 1-10 ---	1-20
P,X	WO 03 017763 A (GOLDSMITH MERRILL ;BATES SUSAN E (US); FOJO ANTONIO (US); KITAZONO) 6 March 2003 (2003-03-06) example 4 --- -/--	1-20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 2003	28/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Skjöldebrand, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internati[illegible] Application No
PCT/JP 03/03823

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KITAZONO MASAKI ET AL: "The histone deacetylase inhibitor FR901228 preferentially enhances adenovirus transgene expression in malignant cells." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 43, March 2002 (2002-03), page 799 XP001152686 93rd Annual Meeting of the American Association for Cancer Research;San Francisco, California, USA; April 06-10, 2002, March, 2002 ISSN: 0197-016X abstract	1-20
X	KITAZONO M ET AL: "Enhanced adenovirus transgene in malignant cells treated with the histone deacetylase inhibitor FR901228" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 61, 1 September 2001 (2001-09-01), pages 6328-6330, XP002957240 ISSN: 0008-5472 the whole document	1-20
X	KITAZONO M ET AL: "Adenovirus HSV-TK construct with thyroid-specific promoter: enhancement of activity and specificity with histone deacetylase inhibitors and agents modulating the camp pathway" INTERNATIONAL JOURNAL OF CANCER, NEW YORK, NY, US, vol. 99, 2002, pages 453-459, XP002957242 ISSN: 0020-7136 the whole document	1-20
X	RICHON VICTORIA M ET AL: "Histone deacetylase inhibitors: a new class of potential therapeutic agents for cancer treatment." CLINICAL CANCER RESEARCH: AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. UNITED STATES MAR 2002, vol. 8, no. 3, March 2002 (2002-03), pages 662-664, XP001152687 ISSN: 1078-0432 page 663, column 2, paragraph 1	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 03/03823

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 03/03823

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02085400 A	31-10-2002	WO 02085400 A1	31-10-2002
WO 03017763 A	06-03-2003	WO 03017763 A1	06-03-2003